FLAX COUNCIL OF CANADA

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD
U.S.A. 20852

RE: Docket No. 91N-0103

Subject: Food Labeling; Health Claims and Label Statements; Request for Scientific Data and Information – Omega-3 Fatty Acids and Coronary Heart Disease

Dear Sirs:

The Flax Council of Canada is responding to the Food and Drug Administration's (FDA's) request for information on the relationship of omega-3 fatty acids and coronary heart disease. The Council believes there is ample evidence that alpha-linolenic acid (ALA), the essential omega-3 fatty acid, has an effect on several physiologic processes related to coronary heart disease (CHD). The Council's specific points are outlined below.

Alpha-Linolenic Acid is an Essential Omega-3 Fatty Acid

In the final rule on health claims and label statements related to omega-3 fatty acids and CHD (*FR* 58, no. 3, January 6, 1993, pp. 2682-2738), FDA indicated that it defined omega-3 fatty acids as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The agency stated that it believed it had "represented the potential nutrient-disease relationship appropriately by limiting its attention to EPA and DHA" (as cited on p. 2683).

The Council disagrees with this conclusion. ALA is an omega-3 fatty acid by definition, being the parent compound of the omega-3 fatty acid family. In the strictest sense, ALA is the essential omega-3 fatty acid, as the human body cannot manufacture it and must acquire it from food. Animal, clinical and epidemiologic research suggests a role for ALA in the prevention and management of chronic diseases, including CHD. For these reasons, the Council believes that the definition of omega-3 fatty acids must include ALA.

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Alpha-Linolenic Acid and Coronary Heart Disease

ALA influences a variety of biologic processes associated with CHD. For example, consumption of ALA affects the composition of cell membrane phospholipids, the metabolism of omega-6 fatty acids, the production of arachidonic acid, the formation of eicosanoids derived from arachidonic acid that promote inflammation and platelet aggregation, and the excitability and beating rate of cardiac myocytes. Research findings related to these biologic processes are described in the sections that follow.

Composition of Cell Membrane Phospholipids

Consumption of flaxseed, which is the richest source of ALA in the North American diet, increases significantly the concentration of ALA, EPA and total omega-3 fatty acids in plasma phospholipids, cholesteryl esters, triglycerides and neutrophils (Cunnane et al., 1993; Layne et al., 1996; Mantzioris et al., 1994). Incorporation of ALA into cell membranes influences membrane flexibility, the release of arachidonic acid and the formation of eicosanoids derived from arachidonic acid.

Production of Eicosanoids Derived from Arachidonic Acid

Some of the eicosanoids derived from arachidonic acid, particularly thromboxane A2, promote platelet aggregation and, hence, increase the risk of thrombosis. Feeding flaxseed oil reduces the formation of thromboxane A2. For example, in one study (Ferretti and Flanagan, 1996), a healthy male subject ate a controlled low-fat diet to which specific vegetable oils (olive + corn oils, canola + flaxseed oils) were added each for a period of seven weeks. The respective vegetable oils provided 95% of all the fat in the diet. During the canola/flaxseed dietary intervention period, the urinary excretion of 11 -dehydrothromboxane B2 (a metabolite of thromboxane A2) decreased 34% from baseline.

In a study of nonhuman primates, feeding ALA at a level of 5.3% of total energy for 14 weeks produced a significant reduction in prostaglandin E2 (PGE2) production by peripheral mononuclear cells. ConA-stimulated PGE2 production decreased 46% (Wu et al., 1996).

Production of Cytokines

Cytokines are proteins synthesized and released by a variety of immune system cells in response to injury, infection or exposure to foreign substances. They both initiate and amplify inflammatory processes. Atherosclerosis is recognized as an inflammatory disease.

In humans, feeding a flaxseed oil-based diet rich in ALA for four weeks significantly reduced the synthesis of tumor necrosis factor and interleukin-1 β. Tumor necrosis factor synthesis was inhibited 74% and interleukin-1 β synthesis was inhibited 80% in these subjects (Caughey et al., 1996). In horses, feeding a diet containing 8% linseed oil for eight weeks significantly decreased endotoxin-induced macrophage production of tumor necrosis factor (Morris et al., 199 1)

Prevention of Arrhythmia

Pure preparations of ALA, EPA and DHA were equally effective in protecting against fatal arrhythmias in dogs. In one study (Billman et al., 1999), intravenous infusion of pure ALA, EPA and DHA reduced significantly the incidence of ventricular flutter-fibrillation and protected a majority of dogs from fatal arrhythmias. Infusion of the control lipid (soybean oil) failed to protect any animals from fatal arrhythmias.

Other work by Drs. Leaf and Kang has shown that free ALA, EPA, DHA, linoleic acid and arachidonic acid effectively prevented as well as terminated toxin-induced arrhythmias in neonatal rat cardiac myocytes (Kang and Leaf, 1996a). In addition, ALA, EPA and DHA slowed the beating rate of isolated neonatal rat cardiac myocytes (Kang and Leaf, 1996b).

Clinical and Epidemiologic Data

In clinical trials, ALA exerts positive effects on blood lipids. One study (Chan et al,, 1991) found dietary ALA was as effective as oleic acid and linoleic acid in lowering plasma total cholesterol, LDL-cholesterol and VLDL-cholesterol in eight healthy men aged 20-34 years. In another study (Bierenbaum et al., 1993), the addition of 15 g milled flaxseed to the daily diet produced significant reductions in blood total cholesterol (-7%) and LDL-cholesterol (- 11%) in 15 hyperlipidemic men and women who had just completed a trial of the effect of vitamin E supplementation on serum lipids and lipid oxidation products. The blood cholesterol lowering effect seen in the latter study may have been due, in part, to the dietary fibre content of flaxseed.

The results of epidemiologic studies suggest that ALA has particular effects related to CHD. Researchers with the Lyon Diet Heart Study hypothesized that ALA may have unique antiarrhythmic and antithrombotic properties that reduce fatal CHD events. All participants in this study had previously survived a myocardial infarction (MD. Those who consumed a Mediterranean-type diet rich in ALA experienced a reduction in MI and cardiac deaths of 70%, without a reduction in blood cholesterol and tryiglycerides, compared with a control group who consumed their usual Western-type diets (de Lorgeril et al., 1994). In an extended follow-up to this study, the protective effect of the Mediterranean diet was maintained. As in the original analysis, ALA-but not EPA and DHA-was significantly associated with protection against recurrence of MI (de Lorgeril et al., 1999).

Data from the Health Professionals Follow-up Study found a specific preventive effect of ALA. An age-adjusted analysis of dietary fat intake and risk of MI among 43,757 men who participated in the 1992 survey, found that ALA as a proportion of total energy was inversely associated with risk of MI and fatal coronary disease. The effect of ALA was independent of other dietary and non-dietary risk factors. MI risk was not associated with the intake of EPA and DHA in this study, suggesting that the cardiovascular effects of ALA differ from those of the long-chain omega-3 fatty acids (Asherio et al., 1996).

In the Multiple Risk Factor Intervention Trial (MRFIT), ALA intake as a percentage of total energy was inversely associated with mortality from CHD, cardiovascular diseases and all causes among subjects assigned to the usual care intervention (Dolecek, 1992). ALA content of blood cholesterol ester and phospholipids was also inversely associated with stroke risk among MRFIT subjects followed for 6.9 years (Simon et al., 1995).

Finally, an analysis of data from the Nurses' Health Study showed that female nurses in the highest quintile of ALA intake had a lower relative risk of fatal and nonfatal MI compared with those in lower quintiles (Hu et al., 1999).

Human Requirements for ALA

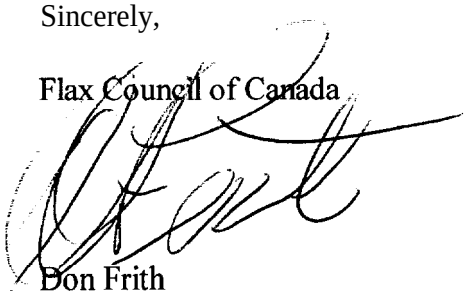
Nutrition experts are beginning to recognize the essentiality of the omega-3 fatty acid family. Although the United States presently has not established a Dietary Reference Intake or Recommended Dietary Allowance for the omega-3 fatty acids, some groups have done so. The international participants at the Workshop on the Essentiality of and Recommended Dietary Intakes for Omega-6 and Omega-3 Fatty Acids, held on the National Institutes of Health campus in April, 1999, recommended an adequate intake level for ALA, EPA and DHA for adults and in infant formula diets (Simopoulos et al., 1999). In addition, the Expert Panel convened by the Life Sciences Research Office to assess the nutrient requirements for infant formulas recommended that infant formulas contain ALA at a minimum of 1.75% of total fatty acids and a maximum of 4% of total fatty acids (LSRO, 1998).

The Council is pleased to have this opportunity to comment on the FDA's request for scientific data and information related to omega-3 fatty acids and coronary heart disease. The Council is available to answer any questions the FDA may have regarding the metabolism and health effects of alpha-linolenic acid.

Thank you.

Sincerely,

Flax Council of Canada



Don Frith
President

DHF/dm

Encla sures

Enclosures:

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